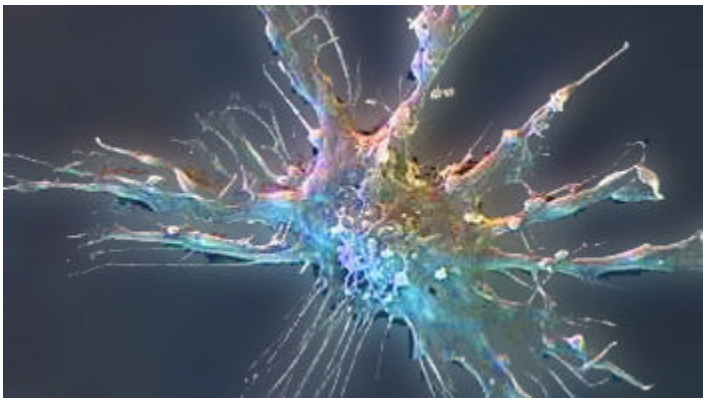
Immunologists Take Home Nobel

The Nobel Assembly announced today that three researchers in the field of immunology will share the 2011 Prize in Physiology or Medicine.

By Rachel Nuwer | October 3, 2011

Link this Stumble Tweet this



A dendritic cell Flickr, AJC1

Today's Nobel Prize in Physiology or Medicine honors work in immunology that provides new avenues for prevention and therapy against infections, cancer, and inflammatory disease.

The Prize is shared by three researchers who have "revolutionized our understanding of the immune system" by discovering the "gatekeepers" of this integral defense mechanism, according to the Nobel Assembly's press release.

Jules Hoffmann, a Luxembourgian based at the University of Strasbourg in France, and Bruce Beutler, an American at Scripps Research Institute in California, share half of the award for discovering receptor proteins that recognize microbes and activate innate immunity. Ralph Steinman, a Canadian cell biologist at Rockefeller University, took the other half of the award for first describing the immune system's dendritic cells and their role in activating and regulating adaptive immunity, the later stage of immune response responsible for clearing microorganisms from the body. Sadly, Steinman passed away last Friday (September 30), before he got word of his crowning achievement.

Steinman's "greatest contribution was that he himself really generated the field of dendritic cell biology," Gerold Schuler, head of the department of dermatology at the University Hospital Erlangen in Germany and Steinman's former post-doc, told *The Scientist* in an email. Schuler says there is "no doubt" that Steinman's work was worthy of a Nobel. The insights Steinman made into dendritic cell biology "are now crucial to understanding and fighting diseases, notably for designing better vaccines," said Schuler.

Jules A. Hoffmann nobelprize.org

Hoffmann and Beutler's work focuses on the first line of defense that destroys invading microbes and triggers inflammation to ward off bacterial, viral, or fungal enemies. In 1996 Hoffmann and colleagues made a pioneering discovery while investigating *Drosophila* with different mutations in *Toll*, a gene associated with embryonic development. When the mutant flies were infected with bacteria or fungi, Hoffmann noticed that they could not mount an adequate immune defense, and quickly died as a result. His observations led him to conclude that the Toll gene product helped sense pathogenic microorganisms and that Toll activation was needed in order to mount defense against the microbial invaders.

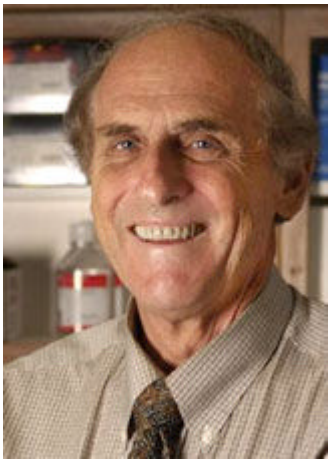
In 1998, Beutler extended his findings to mammals. While searching for receptors related to the bacterial product lipopolysaccharide (LPS) that causes septic shock, a potentially fatal over-stimulation of the immune system, Beutler and his colleagues observed that mice with mutations in a gene quite similar to that in the fruit fly's Toll gene were resistant to shock. The gene turned out to encode the Toll-like LPS receptor, which binds bacterial LPS, resulting in the initiation of an innate immune response. In excess, however, that inflammation can lead to septic shock. Mice with mutant LPS receptors failed to bind LPS and thus never succumbed to shock.

Bruce A. Beutler nobelprize.org

Beutler's work is a rare example of truly exploratory research, said Alexander Poltorak, a mouse geneticist at Tufts University and the lead author on Beutler's groundbreaking 1998 *Science paper* describing LPS signaling and gene mutations. "We didn't have any hypothesis, and that's the beauty of it," said Poltorak, a former postdoc in Beutler's lab. Beutler "absolutely" deserves the Nobel for the research, he added, noting the many subsequent discoveries made possible by Beutler's work. In the past 12 years, for example, scientists have reported about a dozen discoveries of various Toll-like receptors in humans and mice, each of which recognizes certain types of microbial molecules. Mutations in any of these receptors can increase the risk of infections or chronic inflammatory disease.

Steinman's portion of this year's Nobel focuses on a different part of the immune system—adaptive immunity, which occurs when microorganisms make it through innate immunity's first line of defense. The adaptive immune system involves the production of antibodies and killer cells that seek out and destroy infected cells. The adaptive immune system stores immunologic memory for rapid defense mobilization if the same microbes invade in the future.

In 1973, Steinman discovered a new immune cell type present in tissues in contact with the external environment, like skin, that he coined the dendritic cell. He showed in cell culture experiments that the presence of dendritic cells elicited in vivid T cell response to foreign substances, indicating their importance in the adaptive immune response. At first, these findings were met with skepticism by the scientific community, but Steinman's follow-up work put any remaining doubts to rest, conclusively demonstrating that dendritic cells have a unique capacity for T cell activation and play a key role "in conducting the immune orchestra," Schuler said.



Ralph M. Steinman nobelprize.org

Steinman "was stubborn and brave enough to continue working on dendritic cells even though his work was largely ignored—to say the least—for the first 10 years," said Schuler, who co-authored Steinman's description of dendritic cell maturation first published in the *Journal of Experimental Medicine* in 1985. The work led to "an explosion" of research in the field of dendritic cells, Schuler added, and eventually brought the discovery into the clinic.

In fact, Steinman's own life was extended using a dendritic cell-based immunotheraphy of his own design. But the immunologist finally lost his battle with pancreatic cancer last week, just three days before his Nobel achievement was announced. "We are so touched that our father's many years of hard work are being recognized with a Nobel Prize," said Steinman's daughter Alexis in a statement issued by Rockefeller University. "He devoted his life to his work and his family, and he would be truly honored," she said.

"Ralph has changed my life in many ways," Schuler said of his former mentor. "[He was a] deeply caring and understanding human being…. I am very sad that he passed away, notably without having the chance to enjoy becoming a Nobel Laureate."